REMARKS / ARGUMENTS

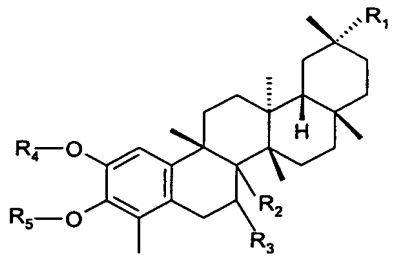
The Examiner's reconsideration and removal of various rejections under Section 112 is acknowledged. In the Final Office Action mailed December 23, 2006, the Examiner has rejected Claims 7 and 8 as either anticipated or obvious in view of a publication showing testing of compounds which have been identified or specified in such claims. In view of such rejection, Claims 7 and 8 will be cancelled upon entry of the instant amendment.

Applicant respectfully requests reconsideration of the final rejection of Claims 9, 10, 11, 12 and 13 in view of the following remarks.

The Invention

As noted in the response to the Office Action mailed July 25, 2006, this invention relates to the design and development of derivatives of celastrol that will retain the benefits of HSR induction and yet are substantially reduced in toxicity.

The invention is in the field of medicinal chemistry, and in particular, the invention relates to analogs and derivatives of nortriterpene quinone methide celastrol represented by the general formulae **III**.



III

- wherein R_1 is H, CH_2OH, COOH, CH_2OCOR wherein R is C-1 to C-12 alkyl, carboxyalkyl, carboxyalkenyl, alkoxycarbonylalkyl, or aminoalkyl;
- wherein R_2 and R_3 are individually H or OH, or together a double bond or epoxide; and

- wherein R_4 and R_5 are individually H, lower acyl, or lower alkyl, or together are a substituted or unsubstituted methylene or ethylene, -CO-, -COCO-, or $-SO_2-$.

Applicant has discovered that these compounds are potent inducers of the heat shock response (HSR). Activators of the HSR in warm blooded animals can be useful in the therapy of neurodegenerative, neoplastic and inflammatory diseases. The invention also relates to the use of these compounds as therapeutically effective in neurodegenerative, neoplastic and inflammatory diseases through the activation of the HSR.
The invention claims benefit from the ability of compounds of the general formula III to induce HSR in the absence of hyperthermia. Such benefits are not associated with any other direct effect, cytotoxic or otherwise, but rather the consequences of the rapid induction of HSR.

Compounds of the general formula III may be administered therapeutically to warm blooded animals orally at a dose level of 0.01 to 10mg per kilogram or parenterally at a dose level of .001 to 1 mg per kilogram.

Therapeutic Benefits of HSR Induction
The HSR has multiple effects on an organism which include the immediate induction of genes encoding molecular chaperones, proteases, and proteins associated with protection and recovery of cell damage. Regulation of protein folding is one aspect, however numerous other benefits are also operative. Recent publications that underscore this diversity were referenced in the Response to Office Action dated November 24, 2006. Additional support is found in the following reports:

Celastrol is a potent inhibitor of amyloid β-peptide production in CHO cells. Inhibition of 90% was found at 0.5 μM concentration. Suppression of NF-κB has been implicated [D Paris, N Patel, A Quadros, M Linan, P Bakshi, G Ait-Ghezala and M Mullan, Neurosci Lett (2006)]. Benefit in the therapy of Alzheimer's disease is supported by these data. Derivatives of celastrol that possess equivalent ability to induce the HSR would possess similar benefit.

Celastrol blocks neuronal cell death and extends life in a transgenic mouse model of amyotrphic lateral sclerosis [M Kiaei, K Kipiani, S Petri, J Chen, NY Calingasan and NF Beal, Neurodegenerative Dis 2:246 (2005)]. Celastrol was administered orally to mice at doses up to 8mg/kg/day for the term of the experiment. Survival was enhanced from 130 to 152 days; no toxicity was observed at the highest dose employed. The authors conclude that celastrol may be useful in the treatment of neurodegenerative diseases, in particular ALS. Derivatives of celastrol that possess equivalent ability to induce the HSR would possess similar benefit.

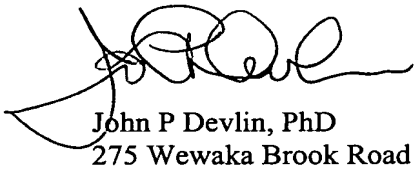
As reported in the Response to Office Action dated November 24, 2006, HSR potentiates TNF-induced apoptosis of tumor cells [W VanMolle et al, Immunity 16:685 (2002); M Leist and M Joattela, Nature Med 8:667 (2002)], It has now been demonstrated that celastrol duplicates such potentiation in the absence of hyperthermia. The mechanism of action, in both instances, is believed to be associated with the suppression of NF-κB activation [G Sethi, KS Ahn, MK Pandey and BB Aggarwal, Blood (2006)]. Again, derivatives of celastrol that possess equivalent ability to induce the HSR would possess similar benefit.

Induction of HSP70 by Derivatives of Celastrol.
Celastrol, its derivatives and chemically related reference compounds were evaluated for their ability to induce expression of an Hsp70-1 promoter-luciferase reporter gene stably integrated into human HeLa cells grown in Dulbecco's modified Eagle's medium with10% fetal calf serum and penicillin/streptomycin. Such expression by celastrol was also found in various cancer cell lines and SH-SY5Y neuronal cells, demonstrating that activation was independent of cell type.
Cells were plated at 7.5×10^3 cells/well in 96 well plates 24 hours before compound treatment. Compounds were prepared at 10mM concentration in DMSO and diluted in medium to the test concentration. Twenty-four hours after compound addition, the cells were harvested for luciferase activity using the Bright-Glo reagent and quantified with a 96-well plate luminometer. The EC_{50} of celastrol was determined to be 3μM. The dose response of celastrol and its derivatives are provided in the original disclosure. Celastrol (3μM) pretreatment also protected (1.7 fold) both HeLa and SH-SY5Y cells from 45°C heat-induced cell death. Full details of these experiments are published [SD Westerheide, JD Bosman, BN Mbadugha, TL Kawahara, G Matsumoto, S Kim, W Gu, JP Devlin, RB Silverman, RL Morimoto, J Biol Chem 279:56053 (2004)].

In view of this, it is respectfully submitted that the compounds herein described present both scaffolds for the development of biologically active compounds that will retain activity and also provide less toxicity than is possible with either celastrol or pristimerin, in addition to being candidates for development in and of themselves. As is described in the specification at page three (3), such compounds have demonstrated biological activity, and Applicant has supplied above additional publications that recite the experimental basis for this disclosure. Additionally, as outlined above, the toxicity profiles are much more favorable than either celastrol or pristimerin.

In view of the foregoing, it is respectfully submitted that the subject application is in condition for allowance and such favorable action at an early date is earnestly solicited.

Respectfully submitted,



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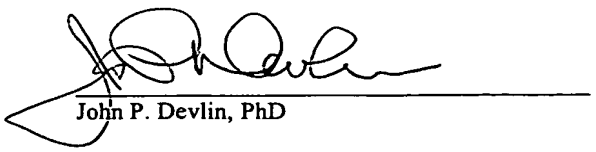

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